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Improving representativeness in trials: a call to action from the Global Cardiovascular Clinical Trialists Forum

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Abstract

Participants enrolled in cardiovascular disease (CVD) randomized controlled trials are not often representative of the population living with the disease. Older adults, children, women, Black, Indigenous and People of Color, and people living in low- and middle-income countries are typically under-enrolled in trials relative to disease distribution. Treatment effect estimates of CVD therapies have been largely derived from trial evidence generated in White men without complex comorbidities, limiting the generalizability of evidence. This review highlights barriers and facilitators of trial enrollment, temporal trends, and the rationale for representativeness. It proposes strategies to increase representativeness in CVD trials, including trial designs that minimize the research burden on participants, inclusive recruitment practices and eligibility criteria, diversification of clinical trial leadership, and research capacity-building in under-represented regions. Implementation of such strategies could generate better and more generalizable evidence to reduce knowledge gaps and position the cardiovascular trial enterprise as a vehicle to counter existing healthcare inequalities.

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Graphical Abstract

Barriers to enrollment of diverse populations and strategies to achieve representative enrollment in cardiovascular clinical trials.

Keywords Clinical trials • Equity, diversity, and inclusion • Health equity • Research equity • Trial representativeness • Trial eligibility

Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, affecting both sexes equally and with a disproportionate burden on older individuals and those living in low- and middle-income countries (LMICs). Trials with relatively homogeneous participants who are at risk of the outcome but have no complex comorbidities can be efficient, provide precise estimates of treatment effect, and maximize the estimated safety of an intervention. Adequate and timely enrollment is important to ensure that trials are completed on time and under budget; this remains a major focus of clinical trialists. However, trials should enroll participants who are representative of those living with the disease to ensure that estimates of treatment effect and safety are generalizable; subgroup analyses to assess for treatment interactions with relevant variables can be undertaken,[1–3] and that communities can benefit from the research infrastructure and quality healthcare facilitated by trials[4,5] There are also ethical and moral arguments for representativeness among research participants.[1–5] Finally, enrolling more representative populations would support the broad and rapid adoption of trial results into communities and lead to more equitable improvement in health (*Figure 1*).

Despite increasing awareness of the importance of representativeness, participants enrolled in CVD randomized controlled trials (RCTs) remain largely homogeneous, leaving certain groups consistently under-represented relative to disease distribution (*Figure 2*).[1,4–10] While timely, efficient enrollment is often seen as a tradeoff in achieving a representative trial population, it does not have to be. This narrative review summarizes the evidence regarding trends in CVD trial enrollment and strategies that may increase representativeness in clinical trial populations.

Under-represented groups in cardiovascular disease trials

Older adults and children

Older adults are underrepresented in CVD trials despite having the greatest burden of CVD and a growing need for evidence-based cardiovascular care.[3] While the incidence of many CVDs increases with age, older adults are commonly excluded from clinical trials due to concerns about comorbidities, drug-drug interactions, and decline in physical and cognitive ability.[3] As a result, clinical decisions are often informed by evidence from trials involving younger, less comorbid patients in whom estimated treatment efficacy and safety estimates may be different. In recent years, there has been no significant increase in enrollment of older adults, with only two large CVD trials specifically targeting older adults with heart failure (HF).[11,12] Furthermore, in a review on pharmacological management of ischemic heart disease, 53% of 839 clinical trials excluded older adults, most commonly over age 75 or 80.[13] Given the later age of onset of CVD and HF in women, exclusion of older individuals may exacerbate the under-enrollment of women in RCTs.[14]

While pediatric cardiac conditions including congenital heart disease and cardiomyopathies have a growing global burden with downstream sequelae, children are underrepresented in cardiovascular trials.

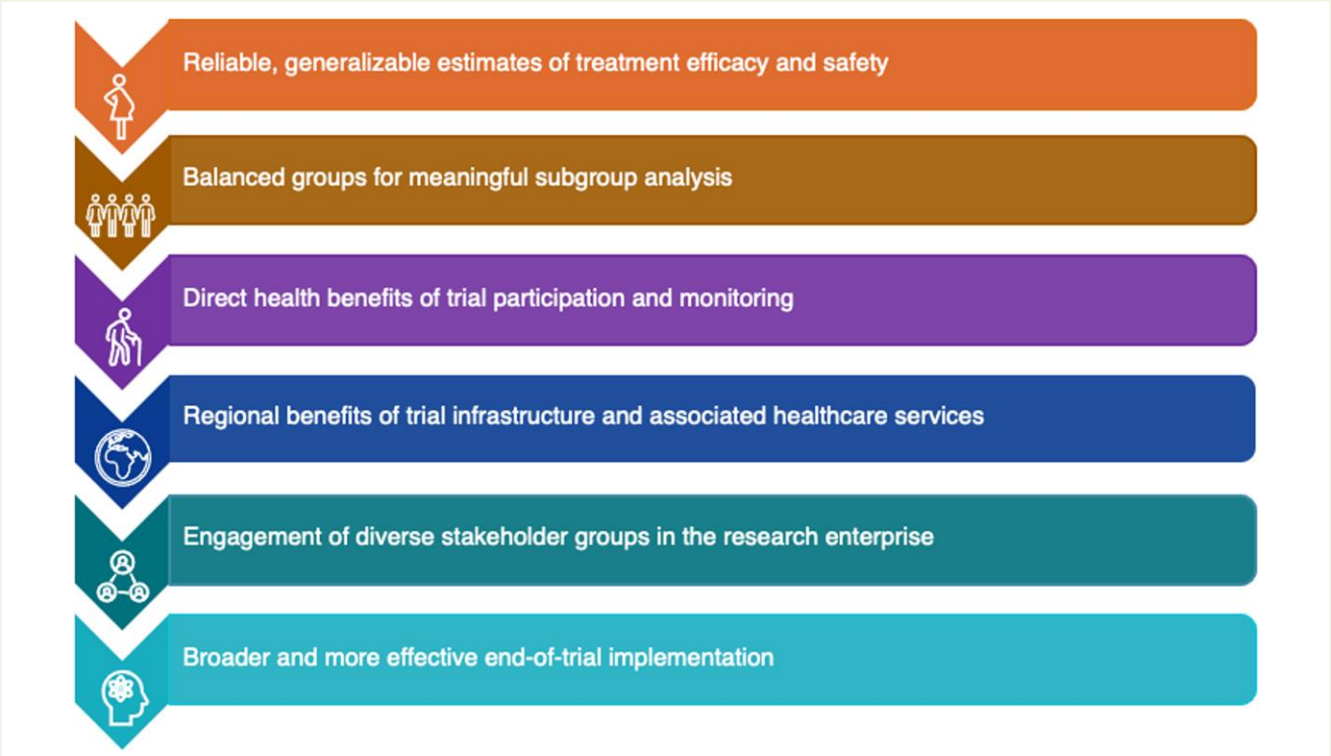

Figure 1 Benefits of representativeness in cardiovascular clinical trials.

Rigorous studies examining the efficacy of medications used in children with heart disease are lacking and most cardiovascular medications are currently not labeled for pediatric use. Less than 25% of Food and Drug Administration (FDA) approved drugs have sufficient pediatric data to support their dosing, safety, and efficacy in children.[15] A study of over 30 000 children hospitalized with cardiovascular conditions revealed that 78% received more than one off-label cardiovascular medication.[16] Treatment decisions in children tend to be based on clinical experience, smaller observational studies, or extrapolation from adult data rather than primary evidence. RCTs are important to establish dosing and to generate evidence on the benefits and toxicities of cardiovascular drugs in children. The reliance on anecdotal evidence and observational data to establish the safety and effectiveness of therapies—and the withholding of possibly effective therapies—puts children at greater risk than does the closely monitored setting of a clinical trial.

People of all ages living with physical and cognitive limitations are also underrepresented in clinical trials.[17] This extends to trials of healthcare services, which may be particularly relevant in people with varying abilities.[17] Further research specific to the gaps in the representation of people with disabilities in CVD research is needed.

Women

Despite widespread acknowledgement of the under-representation of women in CVD clinical trials relative to disease prevalence and the implications on trial generalizability, little progress has been made.[2,4,6,9,18] Between 2000 and 2019, there were no significant changes in the representation of women in HF trials, with women constituting only 25% of total participants, despite accounting for approximately 40% of the disease population.[6] Under-representation of women relative to disease burden also occurred in trials for lipid-lowering therapies in coronary heart disease.[19] The evidence to inform drug, device, and procedural treatment decisions in women is often extrapolated from trials with a large proportion of middle-aged men; effect estimates often do not adequately reflect sex differences in pathophysiology, risk factors, drug metabolism, and coronary artery, cardiac chamber, or vascular size.[4] These sex differences are relevant in treatment responses to medical and surgical interventions, including cardiac or vascular device implantations, coronary revascularization, valve replacement, and arrhythmia ablation; and often surface after years of observational data have accrued from clinical settings.

Pregnant and/or lactating women are not represented in most CVD trials due to outdated protection-by-exclusion ideologies.[1] The exclusion of pregnant and lactating women from trial participation - often automatic and unjustified in the context of the individual trial - leaves them vulnerable, with little high quality data to inform their care. In clinical settings, they are often offered historic treatments based on evidence generated from observational data or from consensus of experts.[20] Indeed, guideline recommendations for most cardiovascular conditions in pregnancy or lactation are informed by level C evidence.[20] To date, pregnant and lactating women remain susceptible to the dual risk of having potentially effective treatments withheld or receiving treatments that may have different efficacy and safety profiles than estimated in the clinical trials that excluded them.

Trial reporting on sex or gender does not include transgender individuals,[21] who are marginalized in clinical care and face a higher risk of poor outcomes due to social factors and gender-affirming hormone therapy.[22] Gender - a psychosocial construct that is self-identified - is rarely enquired about or considered in clinical trials. There remain significant knowledge gaps in treatment effect and health outcomes in gender-diverse individuals living with CVD.

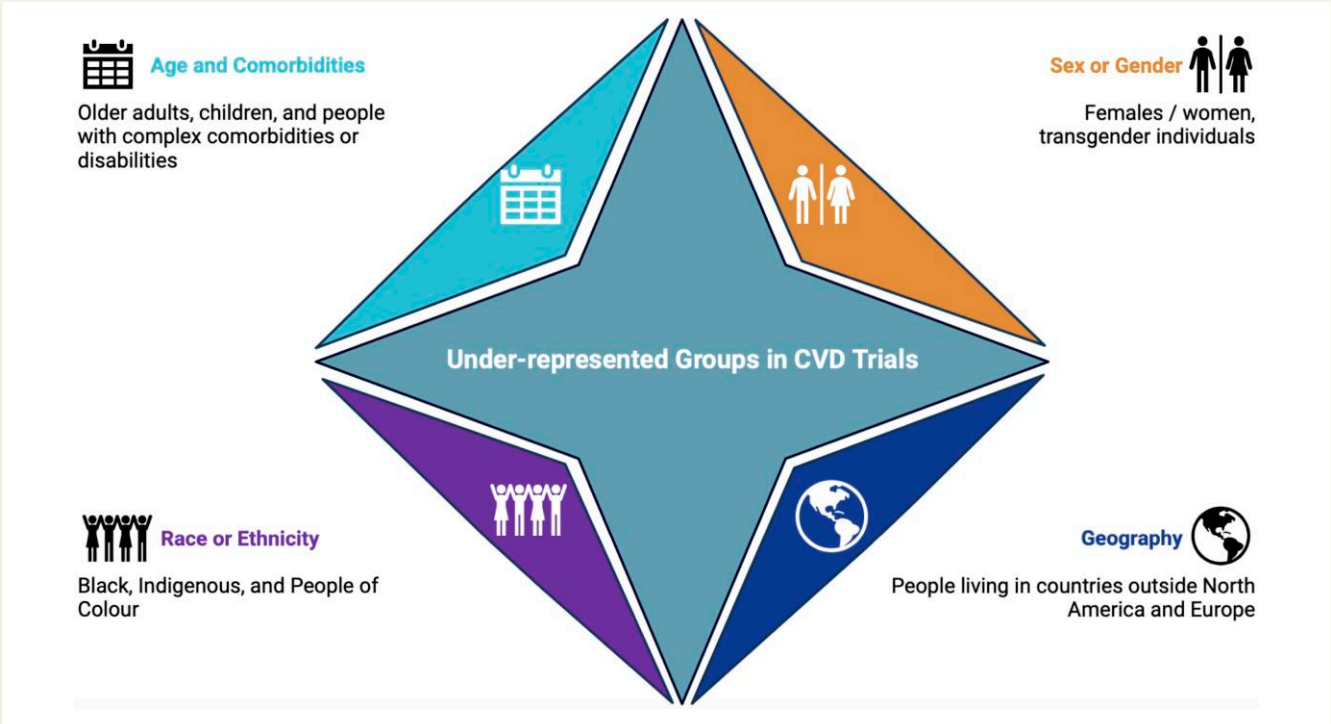

Figure 2 Under-represented groups in cardiovascular randomized clinical trials.

Black, Indigenous, and People of Color

Although many CVDs disproportionally affect Black, Indigenous, People of Color (BIPOC), race and ethnicity data are under-reported and BIPOC participants remain underrepresented in CVD RCTs.[8,9,19,23] Race and ethnicity are primarily social constructs that may influence treatment effects and adverse events via differences in ancestry, comorbidities, socioeconomic status, healthcare access, and quality of care received. There are differences in the metabolism of some drugs due to unique genetic polymorphisms identified across ethnic groups, and these can influence treatment response.[23] For example, Chinese Americans have a higher incidence of angiotensin-converting enzyme inhibitor-induced cough than others in the population.[24] Differences in clotting factors and enzyme mutations impact response to anticoagulants, with evidence suggesting that Asian individuals may require lower doses and Black and Hispanic individuals may require higher doses.[25] These differences highlight the importance of representative enrollment and reporting of race or ethnicity data in clinical trials. However, only a minority of HF and atrial fibrillation trials published in recent years reported race or ethnicity data.[8,26] Among trials that did report race/ethnicity data, BIPOC individuals were consistently under-represented.[8,19,23] A review of acute coronary syndrome RCTs demonstrated that BIPOC individuals accounted for <25% of all enrolled participants.[23] The under-enrollment of BIPOC in cardiovascular drug trials is more pronounced in Europe than in North America; between 2015 and 2016, Black participants accounted for 14.5% of United States-based cardiovascular drug trials and 1.3% of non-US participants (primarily European).[27] These findings are consistent with an analysis of multi-national diabetes trials, which found a 10-fold greater proportion of BIPOC individuals recruited in trials led in North America vs. Europe.[28]

People in low- and middle-income countries

While treatments could translate to the greatest reduction in mortality and morbidity in LMICs, where CVD cases and deaths are the greatest, individuals from these countries are the least represented in CVD clinical trials.[7,29] By engaging centers in LMICs in multinational clinical trials, investigators can expand their research networks, test interventions in lower resource settings, obtain services at lower relative costs, potentially enroll larger volumes of patients per center, improve care by virtue of trial enrollment, and help strengthen research capacity.[7] However, a review examining 414 HF RCTs found that <25% of trials recruited participants from outside Europe and North America and that North America and Europe were overrepresented in trials relative to the global burden of disease.[7] Only 3% of trials recruited participants from Africa, which had the lowest participant-to-prevalence ratio (0.1) among the world's inhabited continents.[7] Without regional evidence, treatment strategies do not adequately account for important differences in risk factors, etiologies, and access to health services, and health decisions are based on studies that are not readily generalizable.[29,30]

Because of limitations in trial reporting, the representation of individuals with intersectional identities that are under-represented in trials, for example, BIPOC women in LMICs, is unknown.

Barriers to representative trial enrollment

There are numerous barriers that may limit the enrollment of certain demographic groups in CVD clinical trials.

Historic marginalization of Black, Indigenous and People of Color

Ongoing mistrust of scientific research discourages some underrepresented communities from participating in trials and engaging with

healthcare systems, although this may vary across countries. The Tuskegee study of the natural history of untreated syphilis in Black men and the propagation of tissue from Henrietta Lacks without consent are just two examples of the harm inflicted on Black people in research.[31] Indigenous people have been similarly harmed by unethical research, including malnutrition experiments in starving children in Canadian residential schools.[31] There is awareness of structural racism in healthcare and research settings, particularly in the USA, but discrimination persists. This perpetuates distrust of research among some demographic groups, likely posing a barrier to clinical trial participation.[31,32]

Recruitment and consent

Recruitment in ambulatory settings is independently associated with the under-enrollment of women in CVD trials,[6] and may be related to sex or gender differences in access to specialized ambulatory care clinics.[4,8] A lack of cultural competence in trial recruitment strategies can also serve as a barrier.[29] For example, participants must often be fluent in English to engage in conversations about trials or consent to trial participation.[1]

The role of consent in the under-representation of specific demographic groups in clinical trials is largely unknown.[15,20] Ethical issues around informed consent by proxy may serve as a particular challenge in pediatric trials;[15] parents may be hesitant to enroll their children due to concerns around allocation to a placebo group with no benefit or to an intervention group with potential harm. Similar fears pertain to pregnant or lactating women, who may decline consent due to possible harm from an intervention to their fetus or breastfeeding child.[6,20]

Eligibility criteria

Restrictive eligibility criteria can limit the participation of equity-deserving groups including older adults, children, and women.[1,6,10,15,19,20] Eligibility criteria are used in trials to select patients who are most likely to respond to intervention and least likely to experience adverse effects, whilst accruing the events required to demonstrate treatment effect to promote trial efficiency. Certain groups of patients must be excluded from trial participation based on the scientifically plausible risk of harm. However, when trial exclusion criteria are too broad and without adequate justification, results may not be generalizable to large portions of the population living with the disease. In RCTs published in major medical journals over a 12-year span, age was the basis of exclusion in 72% of all trials with adults over 65 excluded from 38.5% of trials and children under 16 excluded from 60.1% of trials; age-related exclusion criteria were poorly justified in 78.4% of these trials.[1] Patients were also commonly rendered trial-ineligible due to comorbid conditions like physical disabilities, cognitive impairment, polypharmacy, and visual/hearing deficits that are common in older adults.[1] Additionally, a review of 283 trials published in major medical journals showed that 39% of studies excluded patients on the basis of sex-specific criteria, 10.6% on the basis of communication or language barriers, and 2.1% on the basis of ethnicity.[1] The widespread use of sex-specific exclusion criteria—not only pregnancy and lactation but also the presence of a functioning uterus or the lack of birth control—renders a large subset of women ineligible for clinical trial participation and is independently associated with the under-enrollment of women after adjusting for other trial design factors.[6,20] A review of 317 HF RCTs showed that sex-specific exclusion criteria were present in 81 (26%) trials, none of which provided justification for their use of sex-specific exclusion criteria.[6] These sex-specific exclusions are common even in exercise trials among healthy participants.[33] The widespread conflation of pregnancy with lactation in exclusion criteria is another concern as drugs that may be teratogenic may not be secreted in breast milk, and vice versa. The research paternalism that commonly excludes women in childbearing years from trial participation, regardless of the intervention and regardless of the feasibility of pregnancy, has been accepted without question.[20]

Follow-up processes

Research burden placed on participants can pose financial and social barriers to their participation. The time and cost of attending frequent in-person follow-up visits may be more difficult for individuals who face socioeconomic deprivation, are caregivers to dependents, or who rely on others for transportation.[2,3] Importantly, there is intersectionality between socioeconomic deprivation and under-represented sex and racial or ethnic groups. Lost wages and travel expenses may disproportionately affect these groups.[2,3] These effects may be exacerbated for individuals from rural regions.

Homogeneous trial leadership

The gender and geographic location of trial leaders are independently associated with the composition of trial participants. In a bibliometric analysis of trials published over two decades, men-only trial leadership teams were independently associated with the under-enrollment of women participants relative to trials with at least one woman leader (OR 1.32, 95% CI, 1.12–3.54; $P = 0.047$).[6] In another bibliometric review, trial leadership by at least one woman was independently associated with an 8.4% (95% CI, 1.9%–15%; $P = 0.013$) increase in BIPOC enrollment and twice the odds of reporting race and ethnicity data (OR 2, 95% CI, 1.1–3.8; $P = 0.028$) relative to trial leadership by men-only teams.[6,8] Reasons for this are unclear and may include purposeful attention to cultural competency, inclusion of under-represented groups, and designs that minimize participant research burden in trials led by women, although these need further exploration.[6–8] In another systematic review, trial leadership outside Europe and North America was independently associated with 10-fold odds of enrollment in regions outside Europe and North America, possibly due to greater local access to recruitment pools.[7] Benefits of diverse trial leadership may extend beyond trial representativeness; diverse trialists are more likely to have diverse authorship teams and steering committees,[34] may ask research questions and design trial protocols that address the needs of under-represented populations, and may work to increase research capacity, infrastructure, and human capital in diverse communities.[8,31]

Limited research infrastructure

Inadequate research infrastructure in LMICs and in some rural regions in higher income countries are barriers to trial participation. The World Health Organization found that while 7% of African countries have moderately developed research capacity, >90% have minimal or no research capacity.[30] With insufficient funding, limited electronic health records, biobanks, and data management systems, and public uncertainty in research, there are few locally-led trials to recruit participants in under-resourced regions.[30] Industry sponsors have little incentive to enroll patients in LMICs, even those in which significant progress has been made in research capacity building and regulatory frameworks. While international research collaborations have become more common, some high-income researchers have been criticized for employing a paternalistic 'hit-and-run' research approach in low-income countries without promoting sustainable capacity development, meaningfully involving local investigators, or addressing questions relevant to local populations.[30]

Strategies to increase representativeness of cardiovascular disease clinical trial participants

Despite efforts from regulatory and funding agencies to promote representative enrollment in clinical trials beginning in the 1990s, progress has been slow. The United States FDA has published guidance for sponsors to promote representative enrollment, while the National Institutes of Health (NIH) ties funding to the inclusion of women and diverse racial and ethnic groups in trials.[35–37] Similar guidance documents for representativeness and for sex and gender based analysis have been published in the United Kingdom by the National Institute for Health and Care Research and in Canada by the Canadian Institutes of Health Research.[38–40] Despite these recommendations, trials continue to have inadequate representativeness. Among 142 NIH-funded RCTs published in 2015, only 13% of trials analyzing or reported outcomes by race or ethnicity, and 15% of trials enrolled <30% of women.[41] Temporal trends in the enrollment of women in HF trials published in high impact journals have not changed over 20 years, although enrollment of BIPOC and reporting of results according to sex or gender and race or ethnicity has increased.[6,8,21]

Several multi-level strategies could increase the representative enrollment of participants in CVD RCTs. Importantly, the knowledge gaps in any under-represented group are likely amplified in individuals with overlapping marginalized identities, such as female patients who are BIPOC.[31] As such, trial teams should pay particular attention to including individuals with intersectional identities in clinical trials.

Trial level strategies

Clinical trials can be designed to increase representativeness, with purposeful strategies applied at each trial step. Community-based participatory research and engagement of people with lived experience as research partners and steering committee members can be useful in improving trial design and enhancing trust in the research enterprise. Collaboration with community advisory boards and patient advocacy groups can inform research questions, enhance trial recruitment, and improve knowledge dissemination and implementation in the community.[42]

Recruitment strategies can be designed to promote diversity. Meaningful research partnerships between trial teams, patients, and community organizations can effectively engage under-represented communities, build trust, and address the socioeconomic and cultural factors that influence patient willingness to participate in trials. Recruitment strategies that include digital platforms and community-based settings can aid in diversifying participants. The use of digital communication tools provides opportunities to increase the scale of clinical trials and eliminate barriers created by in-person recruitment. Mobile-application-based recruitment approaches can be effective in increasing gender, race, and ethnicity representativeness.[43] Trial sites can be selected strategically to increase the enrollment of historically marginalized groups. Machine learning algorithms can be used to connect eligible patients to trials through the use of natural language processing which could be used to analyze clinical trial databases and electronic medical records, identify eligible patients based on demographics, and connect them to the right trials.[44] Adaptive enrichment strategies based on interim analysis of who is enrolled could help shift recruitment efforts towards groups that are under-represented.

Input from patient partners could be used to create recruitment materials that are tailored to the cognition, literacy, language, and culture of individuals living with the disease in the region of recruitment; the costs associated with translation can be a deterrent but should be considered an ethical and scientific obligation and accounted for in grant funding requests. Finally, adaptive recruitment strategies, which provide the opportunity to continuously modify recruitment strategies to meet participant diversity targets, could be considered.[2] Prioritizing inclusivity and cultural competence in all study processes and materials may not only enhance diverse enrollment, but also translate to better adherence to the intervention and better trial retention.

Pragmatic and well-justified eligibility criteria can facilitate more representative enrollment.[1] Sex-specific eligibility criteria that broadly render women of childbearing age ineligible should be eliminated; categorical exclusions of pregnancy and lactation should be justified by biological probability or pre-trial evidence of harm.[1,6] Similarly, exclusion criteria based on age and comorbidities should be adequately justified (*Table 1*) and those based on language, race or ethnicity, education level, socioeconomic status, cognitive ability, physical ability, written or spoken language ability, or chronic health conditions should be avoided.[1] When there is uncertainty regarding the safety of intervention in certain populations, experts (e.g. obstetrical specialists for trials involving pregnant women) could be consulted and included in the trial committees.

Consent processes that are carefully designed to match the needs of the participants, accounting for health literacy, language, culture, and level of education, can promote the engagement of diverse individuals. Positive patient- or family-facing interactions in the consent process may help potential participants make better informed decisions regarding trial participation.[15,45] This may be especially important in BIPOC patients, women, and other marginalized individuals who exhibit mistrust in medical research due to systemic discrimination. Digital consent tools can make the research consent process more accessible to some and can be offered based on patient preference.

Efforts can be made to reduce the unique barriers to follow-up that individuals of diverse identities face when participating in clinical trials.[29,30] Consulting with patients, community organizations, and local healthcare workers may provide trial teams with a better understanding of the unique barriers to trial participation and follow-up that some groups face. Solutions for these barriers may include reimbursing participants for costs associated with transportation and childcare, offering flexible clinic hours, utilizing remote follow up when possible, and accommodating individuals with physical and cognitive disabilities. Site-less trials are becoming more popular and rely exclusively on virtual encounters.[46] Trials can be embedded in registries or administrative datasets for clinical outcomes such as death or hospitalization to be determined without research burden on patients.[47,48]

Meaningful analysis and transparent reporting could better inform the care of diverse patients living with the disease. Subgroup analysis and tests for effect modification can provide evidence on whether treatment effects vary by subgroups in the trial population. Demographic characteristics that may affect prognosis or treatment effects should be thoroughly investigated. Tools like the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) can aid this analysis.[49] Trial reporting should include baseline characteristics disaggregated by demographic variables like sex and race/ethnicity. Furthermore, reporting consent rates by demographic variables, and reflecting on potential barriers to consent for different groups may be fruitful in promoting inclusion in future trials.[6,21] Adequate analysis and reporting, along with pooled analyses of conceptually similar trials, may generate more robust and generalizable forms of evidence.

Table 1 Justification scheme for eligibility criteria being considered for an RCT. Adapted from Van Spall HGC, Toren A, Kiss A, Fowler RA. JAMA 2007[1]

Adequate justification for exclusion	Inadequate justification for exclusion
Lack of consent Trial participation is likely to cause harm - There is unacceptable or known risk of harm from the intervention - There is unacceptable risk of harm from withholding the intervention (i.e. allocation to placebo) Individual is unlikely to receive any benefit from the intervention - Individual is unlikely to have the condition of interest or a phenotype that will respond to the intervention - Individual is not at risk for the outcome during the follow-up period - Individual is at imminent risk of death or the outcome (unmodifiable risk) Effect of intervention will be difficult to interpret - Individual is unlikely to adhere to the trial protocol - Individual has a cointervention that will influence the treatment effect - Individual has a comorbidity that will make treatment response difficult to detect	Is not an adequate justification for exclusion AND Exclusion is based on ≥ 1 of the following factors: - Age - Sex - Sex-specific conditions (menstruation, pregnancy, lactation) - Racial, ethnic, or religious background - Spoken or written language ability - Educational background - Socioeconomic status - Cognitive ability or IQ - Physical ability or disability - Chronic health condition

Institutional level strategies

Equal opportunity in academic settings can promote better representation of diverse populations in clinical trial leadership. Diversity amongst trial leaders facilitates gender, racial, and ethnic representation in CVD clinical trials. To harness the strength of women and BIPOC as clinical trial leaders, academic settings should create an inclusive and equitable institutional culture, including research salary support, advancement, and mentorship opportunities to build and maintain capacity for women and diverse researchers (*Figure 3*). By conducting rigorous longitudinal monitoring of inequities within their organizations, institutions can better identify and address gaps that disadvantage women and BIPOC researchers. A culture of respect and accountability not only helps current women and BIPOC in the field but also encourages more diverse learners to pursue cardiovascular research.

Cultural competency training can create trial teams that are well-equipped to understand the unique needs of diverse trial populations.[31] Staff on a culturally competent trial team will understand historical and current health inequities and the ways that research can alleviate them.[31] Cultural humility—reflecting on one's own cultural identity and aiming to unlearn cultural beliefs deeply rooted in global power imbalances—can provide researchers with a perspective that cracks the ethnocentric lens through which Western research is conducted.[31] For example, the trial team testing a digital health intervention spent time understanding the values of African American women at risk of CVD.[50] This involved creating a community advisory board with members from faith-based and community organizations to help with trial design and execution, consulting with community members on appropriate cultural messaging for the intervention, and recruiting participants through churches and community centers.[50]

Training a diverse group of clinical trialists may promote more equitable trials in the future. The CardioVascular Clinical Trialists (CVCT) fellowship program and the US National Heart, Lung, and Blood Institute (NHLBI) support the development of early career researchers from underrepresented backgrounds, providing awardees the opportunity to serve on trial steering committees.[51] Societies such as the American College of Cardiology and American Heart Association as well as catalyst organizations provide diverse investigators with short training courses and networking opportunities. The European Society of Cardiology offers a master's degree in clinical trials, with a focus on applicants from under-represented regions of the world.[10] Individual scientists can make a difference by funding individuals from under-represented regions of the world to train as clinical trialists; the senior author of this manuscript has started such a fellowship program.

Global level strategies

Increasing the representativeness of CVD trials worldwide involves action at the global level to improve infrastructure in regions with low research capacity. Strategies to increase research capacity involve international research collaboration, citizen engagement, and promoting research readiness in the healthcare system.[30] International collaboration that builds sustainable and equitable partnerships can provide better access to funding and technology, improve representative trial enrollment, increase internationally recognized scientific output, and investigate research priorities that are pertinent to the local population.[7,29,30] Global organizations like the CVCT Middle East, Mediterranean, and Africa (CVCT-MEMA) aim to connect stakeholders, promote collaboration, and enhance research capacity in the area. The necessary human capital and expertise to lead CVD trials can be fostered by increasing opportunities for remote research training and fellowships, exchange programs, and visiting professorships. Grants and traveling fellowships from high-income countries, pharmaceutical, and device companies, or professional societies could provide a promising solution to improving local LMIC research capacity.[7,29,30]

Action at the global level should involve a funding policy that incentivizes representative trial enrollment and encourages accountability. Industry and grant funding agencies such as the US NHLBI and Global Alliance for Chronic Disease can ensure more equitable policies by explicitly requiring the inclusion of locally situated investigators for multicenter trials to ensure adequate representation.[51] Although industry sponsors have started to recognize the importance of adequate representation by instating a Chief Diversity Officer, further transparency with clearly outlined goals and responsibilities is required in order to ensure accountability and progress.[30]

A call to action: enrollment and reporting

We call on the global scientific community to prioritize representative inclusion in CVD clinical trials. By implementing strategies throughout

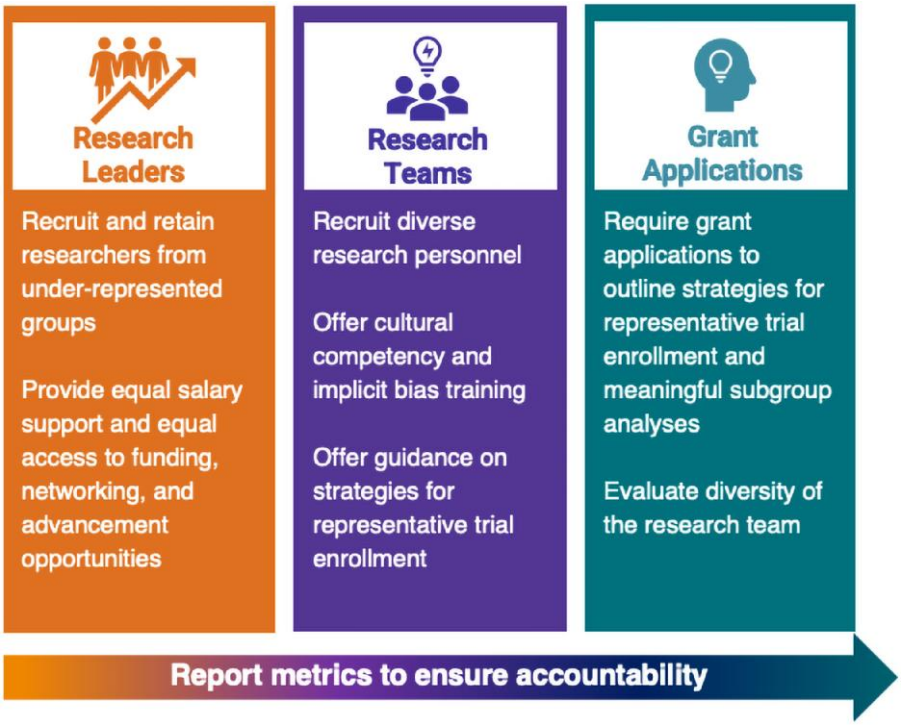

Figure 3 Institutional strategies to improve representativeness in the cardiovascular trial enterprise.

the research enterprise, the CVD clinical trial landscape can become one that serves the entire population equitably. We encourage trialists and institutions to hold themselves accountable to this goal and suggest a 5-year timeframe for clinical trials to achieve representative enrollment with a participant-to-prevalence ratio of 0.8–1.2 for age, sex, and ethnicity in a given region. A participant-to-prevalence ratio in this range ensures that trial participants reflect those living with the disease. Over this time, we advocate for an approach that improves trial design, analysis, and results. Meaningful improvements in trial design first require the identification of key demographic variables pertaining to a research question and evaluation of their potential effect on prognosis and treatment. Trial teams should adopt inclusive recruitment strategies, eliminate unjustified exclusion criteria, and reduce barriers to trial participation. Trials should report results that inform the care of populations living with the disease by reporting baseline characteristics that include sex or gender, race or ethnicity, and regional enrollment. Consent rates could be disaggregated by demographic groups to assess the role of consent in under-representation of some groups.[21] Within the trial analysis, trialists should plan a subgroup analysis of the primary outcome that includes key demographic variables that could modify treatment effect; and use evidence-based tools for analysis like the ICEMAN instrument for robust subgroup analysis.[49] Adverse events should also be disaggregated by sex.[21] Finally, we call upon trialists and institutional leaders worldwide to increase the recruitment of trial participants from under-represented regions by collaborating to promote sustainable research development in LMICs. In the absence of trial representativeness or biological plausibility of different treatment or safety effects in an under-represented group, results should be applied to all demographic groups so that we do not doubly jeopardize underrepresented groups and deprive them of care.

Conclusion

The continued under-enrollment of older adults, children, women, BIPOC, and those from LMIC reduces the generalizability of high-quality RCTs, ultimately exacerbating existing health inequities that negatively impact these populations. Strategies at several levels —global, institutional, and trial—could facilitate more diverse participant enrollment (*Graphical Abstract*). Representativeness in CVD trials could ensure that estimates of treatment efficacy and safety are generalizable, that subgroups are balanced and powered for meaningful analysis, and that there is high-quality evidence to guide treatment decisions in all people, ultimately creating a culture of healthcare justice in cardiology.

Credit statement

H.G.C.V. conceived the manuscript and supervised the work. L.F., J.W.Z., F.D., and H.G.C.V. drafted and edited the manuscript. All authors edited the manuscript and approved the final version.

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Data availability

No new data were generated or analyzed in support of this research.

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Corrigendum

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Corrigendum to: Dual versus single antiplatelet therapy after transcatheter aortic valve replacement: a systematic review and meta-analysis

This is a corrigendum to: R Eikelboom, Y Qiu, K Kim, R Whitlock, E Belley-Cote, Dual versus single antiplatelet therapy after transcatheter aortic valve replacement: a systematic review and meta-analysis, *European Heart Journal*, Volume 43, Issue Supplement_2, October 2022, ehac544.2087, https://doi.org/10.1093/eurheartj/ehac544.2087

In the originally published version of this manuscript, Yuan Qiu's last name was misspelled as "Qui".

This error has now been corrected.